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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/765,244	10/30/97	SEIBEL	P 8484-018-999

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EXAMINER	
LACOURCIERE,K	
ART UNIT	**PAPER NUMBER**
1635	13

DATE MAILED: 07/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/765,244	Selbel
Examiner	**Group Art Unit**
Karen A. Lacourcier	1635

☒ Responsive to communication(s) filed on *Apr 17, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-37 and 39-83* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-37 and 39-83* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

Specification

1. Applicant is advised that the substitute specification filed April 5, 2000 will not be entered because it does not conform to 37 CFR 1.125(b) because: Entry of the substitute specification, as filed on April 5, 2000, would result in the introduction of new matter. For example, on p 28, line 31, the reaction temperature has been amended to read "20°" instead of "20°C", which would introduce the possibility of a reaction temperature of either 20°C or 20°F, or on p 34, line 24, for example, the reaction time has been amended from "60" to "50" min. It is suggested that the Applicant review the substitute specification to avoid the introduction of new matter. Further, it is noted in the marked up copy of the substitute specification numerous "corrections" appear to either remove and replace the same word or actually introduce new errors. It is suggested that the Applicant review the corrections to the specification to verify that the specification should be amended as presented.

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

The specification as filed does not contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78), nor does it contain an abstract of the disclosure as required by 37 CFR 1.72(b) on a separate sheet.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there are amino acid and nucleotide sequences disclosed in the drawings and the text of the specification which are not identified using the appropriate SEQ ID NO: #. The CRF listing of the sequences contained in the instant application has been received and has been entered.

It is noted that the substitute specification submitted does contain both the required priority statement and abstract and does reference sequences by SEQ ID NO:#, however, the substitute specification has not been entered, as stated above, and, as such, the objections made to the specification in the prior Office action based on the priority statement, abstract, Table of Contents, Summary of Invention and sequence references are maintained.

Drawings

2. Applicant is required to submit a proposed drawing correction for figure 6b, to correct the objection noted in the prior Office action, in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Claim Objections

The objection to claim 18 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is maintained.

Claim 18 limits the peptide-nucleic acid chimera of claim 1 to a chimera wherein the peptide "carries a compartment specific recognition sequence". Claim 1 provides a limitation "wherein the signal peptide is specific to a compartment". The signal peptide of claim 1 would inherently have a compartment specific sequence, therefore claim 18 does not further limit claim 1.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-24, 31, 44, 49, 51-65, 68, and 73-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite due to the recitation "capable of".The word "capable of" is indicating the capacity of the chimera to perform a conditional function, which is merely the recitation of a latent characteristic, the scope of which is unclear. Claims 2-24, 54-61, 63-65, 78, 79, 81 and 83 would be indefinite for the same reason, by virtue of their dependence on claim 1.

5. Claim 4 is indefinite due to the recitation "partially palindromic". The term "partially palindromic" in claim 4 is a relative term which renders the claim indefinite. The term "partially palindromic" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, there is no indication of how large a region of palindromic sequence would be required to constitute "partially" palindromic. Claim 5 would be indefinite for the same reasons due to its dependence on claim 4.

Claim 6 is maintained as indefinite due to the recitation "hybridizes". The nucleic acid portion of the chimeric molecule claimed in claim 6 is defined on page 11, paragraph as "hybridizing with itself and comprising no internal homologies". This definition would not allow

one skilled in the art to determine the requisite degree of hybridization in the nucleic acid of the claimed molecule.

Claim 13 is maintained as indefinite due to the recitation "hydroxy/phosphate". It is unclear where the linking group of the claimed molecule is located, although the word "preferably" has been removed by amendment, it is still unclear as to whether the linkage group is required to be at a terminal phosphate or hydroxy group. Therefore, it cannot be determined what chimeras are encompassed by this claim.

Claim 18, as amended, is indefinite due to the recitation "carries a .... sequence". A sequence is a physical descriptor, not a molecule, so it is unclear how a peptide would carry a sequence.

Claim 22, as amended, is indefinite due to the recitation "*at least one* of the signal peptide and the nucleic acid *each* carry". From the wording of this claim, one skilled in the art would not be able to determine whether the claim would encompass chimeric molecules wherein both the peptide and the nucleic acid comprise a functional group or if it is also meant to encompass chimeric molecules wherein only the peptide or only the nucleic acid comprise a functional group.

6. Claim 31 recites the limitation "the plasmid" bridging the first and second lines of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 44 is maintained as indefinite due to the recitation "the ends of the nucleic acid are joined to the peptide by ligation". Claim 44 is dependent on claim 25, which provide the limitation that the ends of the nucleic acid are cyclized. It is unclear how a nucleic acid which is cyclized at both ends could be ligated to a peptide. As such, one skilled in the could not determine what chimeric molecules are encompassed by this claim.

7. Claim 49 recites the limitation "plasmid end" in the third and fourth lines of the claim. There is insufficient antecedent basis for this limitation in the claim.

8. Claim 51 recites the limitation "the molecule DNA" in the second line of the claim. There is insufficient antecedent basis for this limitation in the claim, because it is dependent on claim 25 which does not recite a molecule DNA. Claims 52, 53, 73, 74, and 77 would be indefinite for the same reason, due to their dependence on claim 51.

Claims 51-53, 73, 74 and 77 are further indefinite because the limitations provided by said claims comprise method steps, but are limiting composition claims. It is unclear how a chimeric molecule can comprise a method step, therefore, one skilled in the art would not be able to determine what chimeric molecules are encompassed by these claims.

9. Claim 59 recites the limitation "pretreated cell compartments" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claims 60 and 61 are maintained as rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).Although the applicants appear to be claiming a method, the preamble does not actually state a method. The claims 60 and 61 recite the desired outcome of the process, introducing nucleic acids into cells and organelles, but the claims are actually drawn to the process itself. A process is defined by the steps of the process, but in claims 60 and 61 there are no steps presented which would define the claimed processes. Because the claimed processes are not defined, the claims are indefinite, as one skilled in the art would not know what the processes are.

Claim 62 is indefinite because of the recitation "the ends of the nucleic acid are phosphorylated". Due to the dependence on claim 25 and 44, The nucleic acid referred to in claim 62 is both cyclized and joined to the peptide by ligation. It is unclear how the ends of the nucleic acid are also phosphorylated.

10. Claim 68 recites the limitation "transcription-regulatory sequences" in the second line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 73 is indefinite because it is unclear how a restriction endonuclease can comprise an overhanging end.

Claim 74 is indefinite because it is unclear how a restriction endonuclease can comprise a cleavage site. Claim 74 is further indefinite because of the recitation "preferably" because it is unclear whether or not the cleavage site of the claim is required to be outside of the recognition sequence.

11. Claim 75 recites the limitation "the nucleic acid prior to cyclisation" in second line of the claim. There is insufficient antecedent basis for this limitation in the claim.

12. Claim 76 recites the limitation "the nucleic acid prior to cyclisation" in second line of the claim. There is insufficient antecedent basis for this limitation in the claim.

13. Claim 77 recites the limitation "the molecule sequence" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim.

14. Claim 79 recites the limitation "the position" in second line of the claim. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 80 recites the limitation "the recognition sequences for restriction endonucleases" in second line of the claim. There is insufficient antecedent basis for this limitation in the claim.

16. Claim 81 recites the limitation "the construct" in the sixth line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 82 recites the limitation "the construct" in the fourth line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Response to Arguments

17. Applicant's arguments filed April 17, 2000 have been fully considered but they are not persuasive.

Claims 58-61, 81 and 82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using one specific type of peptide-nucleic acid chimera for the in vitro delivery of a nucleic acid to the mitochondria, does not reasonably provide enablement for methods of use of that peptide-nucleic acid to deliver a nucleic acid to the mitochondria *in vivo*, nor does it reasonably provide enablement for the use of peptide-nucleic acid chimeras to deliver any nucleic acid to any cell or any organelle *in vivo* or *in vitro*. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The rejection of claims 58-61 under 35 U.S.C. 112, first paragraph for not being enabled over the full scope claimed is maintained for the reasons of record set forth in the prior Office action. The rejection of claims 58-61 would further apply to new claims 81 and 82.

With regard to the rejection of claims 58-61, applicants argue that at the time the time the instant invention was made methods of introducing the claimed chimeras into cells were well known in the art such that the claimed methods of introducing a nucleic acid into a cell could be practiced by one skilled in the art over the broad breadth claimed, including in vivo applications. Applicants cite four references as examples of guidance provided in the prior art for delivery of the claimed chimeras.

The references cited by the applicant do not provide any guidance on delivery of a peptide nucleic acid chimera nor do the references cited by the applicant provide any guidance on delivery of any molecule, including a peptide nucleic acid chimera, to a chloroplast or a mitochondria (in vitro or in vivo) as to what mode and composition to use to deliver the peptide-nucleic acid chimera, and how much of the peptide-nucleic acid chimera to administer. The compositions for in vivo delivery of a nucleic acid taught by the cited references would not provide guidance for delivery of a peptide nucleic acid chimera, which is structurally different (by including an amino acid component). The specification teaches the 'particle gun' system, microinjection, electroporation and lipotransfection as modes to deliver the claimed peptide-nucleic acid chimeras, but none of these modes would be applicable for *in vivo* (whole organism) delivery, particularly for a mitochondria, as claimed.

18. The specification does not present any evidence to suggest that a nucleic acid has been delivered *in vivo* to a mitochondria using the methods of claims 58-61, 81 or 82 and does not provide guidelines for doing such. Nor does the field to date have any general guidelines for *in vivo* (whole organism) delivery of nucleic acids to mitochondria using signal peptides. As such, it would require trial and error and undue experimentation for one skilled in the art to practice the methods of claims 58-61, 81 or 82 for *in vivo* (whole organism) applications. Therefore, the rejection of claims 58-61 under 35 U.S.C. 112, first paragraph, is maintained and applies further to new claims 81 and 82, because the specification, while being enabling for in vitro methods of

delivering a nucleic acid to a mitochondria using a peptide nucleic acid chimera, does not reasonably provide enablement for in vivo methods of delivery of a nucleic acid . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

19. Claims 1-37 and 39-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. The rejection of claims 1-37 and 39-61 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for the reasons of record set forth in the prior Office action. This rejection would apply further to new claims 62-83.

Claims 1-37, 39 -61 and new claims 62-83 are drawn to peptide nucleic acid chimeras which comprise a broad genus of signal peptides, but the specification only discloses one members of such genus, a signal peptide specific to the mitochondrial matrix. The specification as filed does not disclose any species of a signal peptide which is specific to a chloroplast, nor does it

disclose any species of a signal peptide for mitochondrial compartments other than the mitochondrial matrix. There is no indication in the specification of how to identify or obtain other members of the claimed genus. Due to the variation in structure (ie amino acid sequence) among members of the claimed genus, one skilled in the art would not recognize that the applicant was in possession of the necessary common features and attributes of the claimed genus, because the one disclosed signal peptide would not be representative of the claimed genus, particularly in regards to a chloroplast signal peptide. The methods claimed in claims 58-61, 81 and 83 is drawn broadly to methods using the claimed chimeras. Due to the lack of adequate written description of said signal peptides, as discussed above, the methods of claims 58-61, 81 and 82 would also lack adequate written description.

21. Applicant's arguments with respect to claims 1-37 and 39-61 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1-7, 9-12, 13, 17-19, 21-24, 54-56, 58-60, 64, 65, 82, and 83 are rejected under 35 U.S.C. 102(b) as being anticipated by Vestweber et al.

Vestweber et al. teach a protein DNA conjugate wherein the c-terminal cysteine of the protein is linked to a DNA molecule via an aminoethyl linker group using a heterobifunctional linkage agent (maleimidobenzoyl-N-hydroxysuccinimide). The protein portion comprises a mitochondrial signal peptide (specifically, yeast cytochrome oxidase subunit IV presequence)which has a reactive cysteine at the c-terminus. The nucleic acid portion is linked at the 5'-terminal hydroxyl group and comprises either a double stranded (which comprises two helical turns) or single stranded DNA 24-mer, which contains regions of complementarity so, therefore, the singlestranded DNA may form a hairpin and said hairpin would include overhanging ends as the ends are not complementary. The DNA is "partially palindromic", as it comprises the sequence "TAAT", which is a four base palindrome. The DNA conjugate is capable of overcoming the mitochondrial membrane by using natural transport mechanisms. Further, the disclosed DNA-protein conjugate is used in a method to deliver a nucleic acid into a mitochondria wherein the conjugate is mixed with pretreated energized mitochondria. The disclosed methods do not include the optional step (c) of claims 54 and 55, but would still anticipate claims 54 and 55, as step (c) is optional.

Claim Rejections - 35 USC § 103

24. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

25. Claims 8, 14-16, 20, 25-37, 39-45, 47, 50, 57, 61-63, 67-71, 77, 79, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vestweber et al. in view of Williams et al. further in view of Latham et al.

Claims 8, 14-16, 25-37, 39-45, 47, 50, 57, 61-63, 67-71, 77, 79, and 81 are drawn to peptide nucleic acid chimeras which comprise a signal peptide specific to mitochondria and methods of delivering a nucleic acid using the claimed chimeras.

Vestweber et al. teach peptide nucleic acid chimeras comprising a mitochondrial signal peptide and methods of delivering said chimeras (see rejection under 35 USC § 102).

Vestweber et al. do not teach the specific limitations wherein the nucleic acid portion of the disclosed chimeras comprise phosphorothioate bonds, mRNA's, transcribable genes, replicatable genes, mitochondrial promoters, cyclized ends, transcription regulation sequences, selection genes (including antibiotic resistance genes), mitochondrial replication origins, regulation sequences, multiple cloning sites, restriction sites (including a BsaI site), particle guns, electroporation, microinjection, lipotransfection, and binding sites for RNA synthesis apparatus.

Williams et al. teach delivery of nucleic acid constructs into a mitochondria in vitro (cell culture), using a signal nucleic acid specific for mitochondria, to introduce genes into mitochondria.

Latham et al. teach phosphorothioate bonds in a peptide nucleic acid chimera.

It would have been obvious at the time the instant invention was made to make a peptide nucleic acid chimera comprising a mitochondrial specific signal peptide, as taught by Vestweber et al., using a nucleic acid which comprises phosphorothioate bonds, mRNA's, transcribable genes, replicatable genes, mitochondrial promoters, cyclized ends, transcription regulation sequences, selection genes (including antibiotic resistence genes), mitochondrial replication origins, regulation sequences, multiple cloning sites, restriction sites (including a BsaI site), particle guns, electroporation, microinjection, lipotransfection, and binding sites for RNA synthesis apparatus because all of the claimed elements would be required to express a gene in a mitochondria, once delivered to a mitochondria, as taught by Williams et al. Further, it would have been obvious to make the nucleic acid portion of the claimed chimera using a phosphorothioate backbone, as taught by Latham et al. to impart greater stability. Phosphorothioate bonds, mRNA's, transcribable genes, replicatable genes, mitochondrial promoters, cyclized ends, transcription regulation sequences, selection genes (including antibiotic resistence genes), mitochondrial replication origins, regulation sequences, multiple cloning sites, restriction sites (including a BsaI site), particle guns, electroporation, microinjection, lipotransfection, and binding sites for RNA synthesis apparatus were all well known in the art at the time the instant invention was made and, further, were all well known as a requirement for gene expression (mRNA's, transcribable genes, replicatable genes, mitochondrial promoters, transcription regulation sequences, mitochondrial replication origins, regulation sequences), for molecular biology purposes (selection genes

(including antibiotic resistence genes), multiple cloning sites, restriction sites (including a BsaI site), for in vitro delivery of nucliec acids (particle guns, electroporation, microinjection, lipotransfection) and for imparting stability to nucleic acids in vivo (cell culture) (phosphorothioate bonds, cyclical ends). One skilled in the art would have been motivated to make a peptide nucleic acid chimera comprising phosphorothioate bonds, mRNA's, transcribable genes, replicatable genes, mitochondrial promoters, cyclized ends, transcription regulation sequences, selection genes (including antibiotic resistence genes), mitochondrial replication origins, regulation sequences, multiple cloning sites, restriction sites (including a BsaI site), particle guns, electroporation, microinjection, lipotransfection, and binding sites for RNA synthesis apparatus in order to deliver and express a gene in a mitochondria, in vitro, in order to replace a mutant copy of said gene, as taught by Williams et al. as preliminary investigations (in vitro) for future gene therapy. One would have been motivated to incorporate the phosphorothioate bonds an cyclized ends to impart greater resistance to nuclease digestion in order to increase the half life of the nucleic acid in cell culture.

Therefore, the invention of claims 8, 14-16, 20, 25-37, 39-45, 47, 50, 57, 61-63, 67-71, 77, 79, and 81 would have bee obvious over Vestweber et al. in view of Williams et al. further in view of Latham et al., absent evidence to the contrary.

26. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Karen A. Lacourciere at telephone number (703)308-7523.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott can be reached at (703) 308-4003. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

George C. Elliott, Ph.D.
Supervisory Patent Examiner
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Karen A. Lacourciere

July 3, 2000